Hemorrhage During Long-Term Anticoagulant Drug Therapy

Part III. The Relationship of Minor to Serious Bleeding

JOHN MARTIN ASKEY, M.D., *Los Angeles*

■ *In a study of reports of 805 instances of spontaneous bleeding occurring among 2,189 patients receiving long-term anticoagulant drug therapy, 124 episodes were considered serious and 681 minor. There was no significant correlation of minor bleeding and serious bleeding.*

Minor bleeding unassociated with excessive reduction of coagulability or an underlying organic lesion could not be considered, according to this evidence, an indication for discontinuance of anticoagulant drug therapy.

In apparently minor internal bleeding, however, hidden underlying organic lesions must be excluded. If gross hematuria occurs, renal lesions must be excluded.

Rectal bleeding must not be considered minor until gastrointestinal lesions have been excluded.

MINOR HEMORRHAGE occurring during long-term anticoagulant drug therapy should be of minor importance *per se*—if the definition is correct. However, minor hemorrhage has acquired a rather sinister connotation to some physicians as a precursor of serious hemorrhage. Its correlation with serious hemorrhage—that which is potentially crippling or fatal—and with serious thrombosis should be clearly and quantitatively documented.

The serious hemorrhages can be broadly divided into two groups: (1) intracranial and gastrointestinal hemorrhages, which make up about 90 per cent of this group; and hemorrhages into various visceral sites, which largely account for the remaining 10 per cent. Minor hemorrhages include purpura, hematomas, episcleral hemorrhage, epistaxis and hematuria—all usually due to capillary breaks.

Ecchymosis and petechiae occurring in the first few days of coumarin drug therapy, especially in women with thrombophlebitis, may be a forerunner of the rare and serious complication of gangrenous infarction and necrosis of the skin and subcutaneous tissues. This has not been reported during long-term therapy.

Discontinuance of the use of anticoagulant drugs is mandatory for serious hemorrhage but it is undesirable for minor bleeding, unless the episodes presage concomitant or subsequent serious hemorrhage. Regardless of the reason for stopping the drugs, an increased incidence of thromboembolism

This article on Hemorrhage During Long-Term Anticoagulant Drug Therapy is in five parts. Part IV is scheduled to appear in the April issue.

Submitted 7 July 1965.

may occur within a short period.[4,12,24] The precise mechanism is controversial.

If, in addition to stopping the drugs, vitamin K1 is given, the risk of thromboembolism is heightened. Even with the bleeding extensive and the prothrombin activity excessively low, intravenous vitamin K1 may at times swing the coagulability to so high a level that fatal thrombosis ensues.[7]

The clinician might well ask, what is the importance of minor bleeding in heralding concomitant or subsequent serious bleeding? And, what is the importance of minor hemorrhage in initiating serious thrombosis if the drug is discontinued?

In the early days of anticoagulant drug treatment, the early detection of minor hemorrhage was an indication for stopping therapy. A positive microscopic or chemical finding of hematuria was regarded as a potential precursor of serious bleeding.

Fuller[6] regarded any sign of a bleeding tendency, however slight, as serious and its early recognition of great importance. He recommended the routine use of orthotolidine (occult test) for the detection of microscopic hematuria.

Even more recently, minor bleeding has been regarded as ominous. Lempert[11] warned of "slight bruising, even the slightest sign of hemorrhage, a little epistaxis or a little discoloration of the urine," saying that "presumably, this coincides with sudden profound changes in the thromboplastin factor or other factors."[11] At present, in most large clinics, anticoagulant drugs are not discontinued for more than a day or two at the most for minor hemorrhage, unless the prothrombin activity is excessively reduced. The definition of a "minor" non-threatening hemorrhage may depend, of course, on the apparent clinical severity. Often, neither the physician nor the patient considers diffuse purpura, petechia, ecchymosis, episcleral hemorrhage, hematomas or hematuria to be "minor."

Prandoni and Wright[21] when administering the drug for the first time in 1942, were naturally alarmed by subcutaneous hematomas and hematuria and "lost much sleep over this." Their experiences led to a fortunate delay in the release of the drugs until further studies could be carried out. The inclination to discontinue the drugs and administer vitamin K1 often may still be strong, but the risk of serious thromboembolism after stopping anticoagulant drugs for minor hemorrhage may be as great as the risk after stopping the drugs for major bleeding. Sise[24] reported that "even after relatively minor bleeding such as hematuria and a small hematoma, fatal complications were observed."

Marshall[12] and Conrad and Rothermich[4] observed cerebral and coronary thrombosis as complications after stopping the drugs for bleeding.

How often minor hemorrhages portend concomitant or subsequent serious hemorrhage has not been adequately documented. Even those who strongly advocate the use of the orthotolidine test to detect microscopic hematuria have demonstrated no significant relation of the bleeding to serious hemorrhage.[6,18] Capillary fragility tests are of little value in predicting a tendency to serious bleeding from anticoagulant drugs.[22] The primary and secondary bleeding-time tests on capillaries of the skin described by Owren[15] have not been proved to correlate with the incidence of intracranial and gastrointestinal hemorrhages.

In a previous study of long-term anticoagulant therapy of 1,626 patients, 86 of 95 serious hemorrhages (90 per cent) were either intracranial or gastrointestinal.[1] The other nine were from various sites. No deaths occurred from renal hemorrhage, although hematuria is common.

Material

I have analyzed all the spontaneous hemorrhages in a number of group studies involving 2,189 patients on long-term anticoagulant therapy in which data were given permitting answers to the following questions:

- How many serious hemorrhages were preceded by or were concomitant with minor hemorrhages?
- How many minor hemorrhages occurred without any associated serious hemorrhages?
- Was there any significant correlation between minor and serious hemorrhages?

The answers to these questions should furnish more precise evidence as to whether minor hemorrhages should be a guide as to subsequent serious bleeding.

Results

The serious hemorrhages were considered those of intracranial or gastrointestinal origin or those from other sites known to be capable of killing

TABLE 1.—*Relation of Spontaneous Serious Bleeding to Minor Bleeding in Long-Term Anticoagulant Therapy*

Authors	Number of Patients Treated	Number of Spontaneous Bleeding Episodes	Number of "Serious" Episodes	Associated Minor Bleeding Pre-existing or Concomitant
Tulloch and Wright[27]	227	68	9	No correlation mentioned
Thomes, Scallen and Savage[26]	312	95	17	None
Pollard and coworkers[20]	139	61	10	None
Nichol and Borg[14]	78	41	6	None
Suzman, Ruskin and Goldberg[25]	82	12	2	None
Keyes, Drake and Smith[10]	121	54	5	None
Pickering[19]	195	48	5	None
Bjerkelund[2]	119	53	12	None
Fisher[5]	195	78	15	None
Groch et al.[8]	92	19	12	None
Borchgrevink[3]	103	10	3	None
Waaler[28]	275	54	14	None
Peyman[18]	34	18	0	None
Fuller[6]	217	194	14	None
Total	2,189	805	124	None

or disabling. Among 2,189 patients on long-term anticoagulant treatment, there were 805 spontaneous bleeding episodes (Table 1). Of these, 681 were considered to be minor and 124 serious (5.6 per cent of the overall group). In none of the 124 serious episodes was there specific mention either of minor bleeding preceding the hemorrhage or of any concomitant minor bleeding. Although minor bleeding may have been present and not mentioned, it is probable that all bleeding sites were reported.

Bjerklund,[2] on the contrary, in commenting on 53 instances of spontaneous bleeding, said specifically that there were no cases in which there was bleeding from several places at once.

None of the 681 minor hemorrhages progressed into serious bleeding. There was no significant correlation between minor and serious diffuse hemorrhage from toxic disease.

This in no way excludes the possibility of both minor and serious hemorrhage occurring simultaneously from prolonged toxic doses. Isolated cases attest this danger.

Poisonous doses of the coumarin drugs can induce the same kind of serious diffuse hemorrhagic disease in man that led to the discovery of the drug in the hemorrhagic sweet clover disease in cattle. Prandoni and Wright[21] in their early studies with Dicumarol® found that three patients had hematemesis in association with minor hemorrhages resulting from excessive dosage. Pastor, Resnick and Rodman[17] reported several instances of diffuse hemorrhage due to prolonged excessive doses of anticoagulant drugs. In these patients, hematuria, ecchymosis and hematomas were associated with hematemesis following long periods of excessive dosage.

Most of the superficial capillary hemorrhages occurring with non-poisonous doses do not herald serious hemorrhage. Nontoxic doses seldom cause serious spontaneous hemorrhage except in the presence of a pre-existing bleeding lesion. Hematuria, the commonest minor hemorrhage, seldom requires more than reduction of the dose of coumarin drug or, at most, discontinuance for one or two days.

Owren[16] said he never gives vitamin K1 or a blood transfusion for hematuria, holding that because of the abrupt high coagulability induced, this treatment "is more dangerous than the bleeding." All minor bleeding arising internally, however, should be investigated to exclude internal lesions. Although nearly all the instances of hematuria are due to superficial capillary bleeding, the need for investigation for an underlying causative lesion is not lessened. Mild to moderate bleeding may arise from renal calculi. Gross hematuria, especially if it occurs with a desirable prothrombin level, may unmask a pathologic lesion. Hemley, Arida and Schwartz[9] reported two such instances, one in a patient with a polycystic kidney with multiple small papillary adenomas and the other in a patient with a hypernephroma. In answer to a questionnaire, Nathan and Kimball[13] received reports of 71 occult malignant renal tumors detected during anticoagulant drug therapy. In all patients with hematuria, a renal study is advisable. Thorough investigation is also indicated for rectal

bleeding. Apparent minor bleeding may unmask a carcinoma.[13,23] Although sigmoidoscopic examination is indicated for all patients having a complete physical examination, and especially for patients who are to be given long-term anticoagulant drug therapy, frequently it is not done.

1930 Wilshire Boulevard, Los Angeles, California 90057.

REFERENCES

1. Askey, J. M.: Hemorrhage during long-term anticoagulant therapy. To be published.

2. Bjerkelund, C. J.: The Effect of Long-Term Treatment with Dicumarol in Myocardial Infarction, Grune & Stratton, Inc., 1957.

3. Borchgrevink, C. F.: Long-term anticoagulant treatment in angina pectoris and myocardial infarction, Acta Med. Scandinav. Suppl. 359, Accomp. Vol. 168, 1960.

4. Conrad, F. G., and Rothermich, N. O.: A clinicopathological study of acute myocardial infarction and the role of anticoagulation therapy, Arch. Int. Med., 103:421, March 1959.

5. Fisher, C. M.: Anticoagulant treatment in cerebral thrombosis and cerebral embolism, Neurology, 11:119, April 1961.

6. Fuller, J. A.: Experiences with long-term anticoagulant treatment, Lancet, 2:489, 3 October 1959.

7. Griffith, G. C., Leck, D., and Hegde, B.: Conservative anticoagulant therapy of acute myocardial infarction, Ann. Int. Med., 57:254, August 1962.

8. Groch, S. N., McDevitt, E., and Wright, I. S.: A long-term study of cardiovascular disease, Ann. Int. Med., 55:358, September 1961.

9. Hemley, S. D., Arida, E. J., and Schwartz, N. J.: Occult lesions discovered during anticoagulant therapy, J.A.M.A., 117:153, July 1961.

10. Keyes, J. W., Drake, E. H., and Janney-Smith, F.: Survival rates after myocardial infarction with long-term anticoagulant therapy, Circulation, 14:254, August 1956.

11. Lempert, H.: Discussion: Treatment from a pathologist's point of view. Symposium on anticoagulant therapy, Harvey and Blythe, Ltd., 1961, p. 94.

12. Marshall, J.: Rebound phenomena after anticoagulant therapy in cerebrovascular disease, Circulation, 28:329, September 1963.

13. Nathan, D. A., and Kimball, S. G.: The detection of occult tumors. Anticoagulant Therapy of Ischemic Heart Disease, Grune & Stratton, New York, 1965, p. 119.

14. Nichol, E. S., and Borg, J. F.: Long-term Dicumarol® therapy to prevent recurrent coronary artery thrombosis, Circulation, 1:1097, May 1950.

15. Owren, P. A.: Critical study of tests for control of anticoagulant therapy. Progress in coagulation, Trans. of Conf., International Comm. on Blood-clotting Factors, Friedrich-Karl Schattauer: Verlag, Stuttgart, 1961, p. 294.

16. Owren, P. A.: Symposium on anticoagulant therapy, Harvey and Blythe, Ltd., 1961, p. 238.

17. Pastor, B. H., Resnick, M. E., and Rodman, T.: Serious hemorrhagic complications of anticoagulant therapy, J.A.M.A., 180:747, 2 June 1962.

18. Peyman, M. A.: The significance of haemorrhage during treatment of patients with coumarin anticoagulants, Acta Med. Scandinav. Suppl. 339 (Accomp. Vol. 162), p. 1-62, 1958.

19. Pickering, G. W.: Clinical Problems and Results. Controlled Clinical Trials, Charles C Thomas, Springfield, 1960, p. 115.

20. Pollard, J. W., Hamilton, M. J., Christensen, N. A., and Achor, R. W. P.: Problems associated with the practical management of long-term anticoagulant therapy, Circulation, 25:311, 1962.

21. Prandoni, A., and Wright, L. S.: The anticoagulants, Heparin and Dicoumarin (3. 3 methylene-bis, 4, hydroxycoumarin), Bull., New York Acad. Med., 18: 433, 1942.

22. Ratnoff, O. D.: Bleeding Syndromes, Charles C Thomas, Springfield, 1960, p. 26.

23. Saslow, M. S., and Rosenberg, A. E.: Dicumarol® as indicator of secondary disease, J. Florida Med. Assoc., 37:631, April 1951.

24. Sise, H. S., Moschos, C. B., Gauthier, J., and Becker, R.: The risk of interrupting long-term anticoagulant treatment, Circulation, 24:1137, November 1961.

25. Suzman, M. M., Ruskin, H. D., and Goldberg, B.: An evaluation of the effect of continuous long-term anticoagulant therapy on the prognosis of myocardial infarction, Circulation, 12:338, September 1955.

26. Thomes, A. B., Scallen, R. W., and Savage, I. R.: Value of long-term anticoagulant therapy in coronary disease, J.A.M.A., 176:181, 22 April 1961.

27. Tulloch, J., and Wright, I. S.: Long-term anticoagulant therapy. Further experiences, Circulation, 9:823, June 1954.

28. Waaler, B. A.: The effect of permanent anticoagulant treatment on symptoms and morbidity in angina pectoris, Acta Med. Scandinav., 157:289, 1957.